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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,357	07/13/2006	Moshe Baru	27048U	1205

20529 7590 09/04/2007

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ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
09/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,357	BARU ET AL.	
	Examiner	Art Unit	
	Julie Ha	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-52* is/are pending in the application.

4a) Of the above claim(s) *44,45,48,49 and 52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-43, 46,47,50 and 51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Election/Restriction filed on June 11, 2007 is acknowledged. Claims 28-52 are pending in this application.

Election/Restriction

1. Applicant's election without traverse of species granulocyte colony-stimulating factor (G-CSF) for protein election and multiple sclerosis as the disease in the reply filed on June 11, 2007 is acknowledged. Claims 44-45, 48-49 and 52 are withdrawn from further consideration as being drawn to nonelected species. Claims 28-43, 46-47 and 50-51 are examined on the merits in this office action.

Objection-Minor Informalities

2. The title is objected to because the title is too long. The title is limited to 2-7 words maximum. A new title is required that is clearly indicative of the invention to which the claims are directed.

Rejection-35 U.S.C. 112, 1st

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 28, 47, 50 and 51 are rejected are under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hemophilia, does not reasonably

provide enablement for any other diseases, disorder or conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a method of treatment of a patient suffering from a disease comprising administrating to the patient a pharmaceutical composition of protein or polypeptide and colloidal particles.

(2) The state of the prior art:

The Merck manual indicates that there are plethora of disorders known, for example, Anorectal, foot and ankle, vascular, joint, mediatinal and pleural, arrhythmias and conduction, valvular, peripheral arterial to name just a few (see Merck

manual, Disorders enclosed). Additionally, the Merck manual indicates that there are numerous numbers of diseases, for example, diverticular, bullous, tubulointerstital, prostate diseases, coronary artery diseases, viral skin diseases, inflammatory bowel disease, cystic kidney disease, Alzheimer's disease, Parkinson's disease, Wilson's disease to name just a few (see Merck manual, Diseases enclosed). For example, Alzheimer's disease according to the Merck manual is chronic, global, usually irreversible deterioration of cognition. The main types of Alzheimer's disease are: vascular dementia, Lewy body dementia, frontal-temporal dementias, and HIV-associated dementia (See Merck manual, "Dementia", Etiology and Classification, 2nd paragraph). Furthermore, Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, beta-amyloid deposits, and neurofibrillary tangles in the cerebral cortex and subcortical gray matter (see Merck manual in Dementia under "Alzheimer's disease). Furthermore, the Merck manual indicates that most cases are sporadic, with late onset and unclear etiology (see Merck manual, "Alzheimer's disease", Etiology and Pathophysiology). Since symptoms, signs are similar to those of other dementia, distinguishing Alzheimer's disease from other dementias is difficult (see Merck Manual, "Alzheimer's disease", Symptoms, Signs, and Diagnosis). Furthermore, Mattson MP (Nature, 2004, 430: 631-639) indicates that the risk of Alzheimer's disease (AD) dramatically increases in individuals beyond the age of 70 (see p. 631, left column, 1st sentence). The vast majority of cases of AD are sporadic, they do not run in families...molecular genetic analyses suggest that there are likely many genes that influence one's susceptibility to AD (see p. 633, left column, 2nd

paragraph). Additionally, Mattson indicates that although drugs can temporarily improve memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process (see abstract).

The art recognizes that there are countless different conditions, disorders and diseases, but does not provide how to determine the individuals who are susceptible to any disorder, condition or disease list provided by the Merck manual.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Applicant's activity is based on the determination of predicting those who are susceptible to disorders, conditions and diseases. Since the activity is based on determining the patient population that is susceptible to disorders, conditions and diseases, the predictability in the art is low. This is due to the fact that the art has recognized that there are plethora of different conditions, disorders and diseases, but does not provide how to determine the individuals who are susceptible to any disorder, condition or disease list provided by the Merck manual. For example, not all elderly people over 65 years of age suffer from Alzheimer's disease. Additionally, not everyone suffers from prostate cancer or AIDS.

As described above, Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, beta-amyloid deposits, and

neurofibrillary tangles in the cerebral cortex and subcortical gray matter (see Merck manual in Dementia under "Alzheimer's disease). Furthermore, the Merck manual indicates that most cases are sporadic, with late onset and unclear etiology (see Merck manual, "Alzheimer's disease", Etiology and Pathophysiology). Since symptoms, signs are similar to those of other dementia, distinguishing Alzheimer's disease from other dementias is difficult (see Merck Manual, "Alzheimer's disease", Symptoms, Signs, and Diagnosis). Furthermore, Mattson MP (Nature, 2004, 430: 631-639) indicates that the risk of Alzheimer's disease (AD) dramatically increases in individuals beyond the age of 70 (see p. 631, left column, 1st sentence). The vast majority of cases of AD are sporadic, they do not run in families...molecular genetic analyses suggest that there are likely many genes that influence one's susceptibility to AD (see p. 633, left column, 2nd paragraph). Additionally, Mattson indicates that although drugs can temporarily improve memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process (see abstract).

The claims don't identify the type of disorder, condition or disease or the patient population, therefore, the claim implies that anyone can be protected against any disorder, condition or disease. However, the Applicant has not shown who will be susceptible to disorder, condition or disease and the types of disorder, condition or disease. There are too many variables between the patient populations, thus, it clearly shows the unpredictability of the art.

(5) The breadth of the claims:

The claim is drawn to a method of treatment of a patient suffering from a disease comprising administrating to the patient a pharmaceutical composition of protein or polypeptide and colloidal particles.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

Although the specification provides guidance on how to make the composition and administer the compound, it is unclear as to when to administer the compound and the patient population. The specification discloses that hemophilia A are prone to frequent hemorrhages as a result of one or more misfunctions of the coagulation system (see p. 1, lines 6-7). The specification discloses that one of the causes of hemophilia is a shortage of Factor VIII in the blood and this problem can be treated with Factor VIII concentrates; however, in about 15% of the patients that occurrence results of Factor VIII neutralizing antibodies, so-called inhibitors, whereby a therapy with Factor VIII concentrates is hardly possible (see p. 1, lines 7-11). The specification discloses SCC injection of liposome-formulated G-CSF into mice, and pharmacokinetic parameters were calculated for each mouse (see p. 15, lines 8-13). Furthermore, the specification discloses the pharmacokinetic parameters following IV injection of Factor IX or PEGylated liposome-formulated Factor IX into mice (see p. 15, line 15). The specification further discloses the biological activity of factor VIII that was formulated in-vivo with PEGylated liposomes by injection of liposomes 1 hour after the injection of

unformulated factor VIII in hemophiliac mice. The specification discloses that the results indicate that the half-life and are under the curve of factor VIII that was formulated in vivo with PEGylated liposomes were higher than that of free FVIII (see Example 11). Additionally, the specification discloses that factor VIIa is generally used to treat hemophilia patients with inhibitors and to stop trauma bleeding. FVIIa formulated with PEGylated liposomes were injected into mice, and the rats were bled at various times post-injection and VFIIa activity was measured by a clotting assay and the results indicate that the half-life and are under the curve of FVIIa that was formulated in-vivo with PEGylated liposomes were higher than that of free FVIIa (see Example 13). There are not enough working examples for guidance. For example, as explained above, the specification only describes treatment of hemophilia, utilizing factor VIII, IX and VIIa.

The specification has not provided guidance in the way of a disclosure to how to determine individuals that need protection against any disorder, condition or disease. The specification discloses that the invention is particularly suited to patients previously diagnosed with prostate cancer. The specification discloses that the non-natural amino acid polypeptides, modified or unmodified, can be administered directly to mammalian subject by any of the routes normally used for introducing a polypeptide to a subject (see paragraph [0955]). Furthermore, the specification discloses that the effective amount of the formulation to be administered in the treatment or prophylaxis of disease (including but not limited to cancers, inherited diseases, diabetes, AIDS, or the like) (see paragraph [0951]). As described above, Alzheimer's disease causes progressive cognitive deterioration and is characterized by senile plaques, beta-amyloid deposits,

and neurofibrillary tangles in the cerebral cortex and subcortical gray matter (see Merck manual in Dementia under "Alzheimer's disease). Furthermore, the Merck manual indicates that most cases are sporadic, with late onset and unclear etiology (see Merck manual, "Alzheimer's disease", Etiology and Pathophysiology). Since symptoms, signs are similar to those of other dementia, distinguishing Alzheimer's disease from other dementias is difficult (see Merck Manual, "Alzheimer's disease", Symptoms, Signs, and Diagnosis). Furthermore, Mattson MP (Nature, 2004, 430: 631-639) indicates that the risk of Alzheimer's disease (AD) dramatically increases in individuals beyond the age of 70 (see p. 631, left column, 1st sentence). The vast majority of cases of AD are sporadic, they do not run in families...molecular genetic analyses suggest that there are likely many genes that influence one's susceptibility to AD (see p. 633, left column, 2nd paragraph). Additionally, Mattson indicates that although drugs can temporarily improve memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process (see abstract). Since there are numerous different disorders, conditions (associated with different disorders and diseases) or diseases, there is not enough guidance to determine who is susceptible to certain disorder, condition or disease and when to administer the polypeptide.

There is no clear guidance as to how to determine the patient population, since not all people suffer from the same disorder, condition or disease. Since art recognizes that there are countless different conditions, disorders and diseases, but does not provide how to determine the individuals who are susceptible to any disorder, condition or disease list provided by the Merck manual, more guidance is necessary.

(8) The quantity of experimentation necessary:

In order to treat a disease, a dosage, the subject and regimen must be identified. In order to ameliorate a disease symptoms or conditions, the end point of the treatment also needs to be identified. Since it is uncertain to predict the patient population who are susceptible for unknown disorder, condition or disease, and the Applicant have not provided the appropriate time frame at which the compound should be administered, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the compound would be effective in treating an adult, child, or an infant from all disorder, condition or disease.

Rejection-35 U.S.C. 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 28-43 and 46 rejected under 35 U.S.C. 103(a) as being unpatentable over Martin et al (US Patent # 5225212) in view of Collins et al (US Patent # 5874075) and Zalipsky S (US Patent # 6586001).

9. The instant claims are drawn to a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a protein or polypeptide and colloidal particles, said particles comprising approximately 1-20 mole percent of an amphipathic lipid derivatized with a biocompatible hydrophilic polymer, wherein said protein or polypeptide is not encapsulated in said colloidal particles.

10. Martin et al teach a liposome composition for extended release of a therapeutic compound in to the bloodstream (see abstract). This meets the limitation of claim 28 in part. The liposomes are composed of vesicle forming lipids (phospholipids, such as phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidic acid (PA), phosphatidylinositol (PI) and the like) (see column 5, lines 61-66). This meets the limitations of claims 32-33 and 36-37. The reference further teaches that the liposomes

are between 1-20 mole percent of vesicle-forming lipid derivatized with hydrophilic polymer, having sizes in a selected size range between 0.1 and 0.4 microns, and contain the therapeutic compound in liposome-entrapped form (see abstract). This meets the limitations of claims 28 (in part) and 29-31. The reference further teaches that a biocompatible hydrophilic polymer is polyethylene glycol having a molecular weight between about 1,000-5,000 daltons, and the polymer is derivatized with the polar head group of phospholipids, such as PE (see column 3, lines 1-16 and claims 5 and 6). Additionally, the reference discloses that hydrophilic polymer is exemplified by polyethylene glycol (PEG), polylactic acid, and polyglycolic acid, all of which are readily water soluble, can be coupled to vesicle-forming lipids, and are tolerated in vivo without toxic effects (see column 5, lines 39-43). This meets the limitations of claim 39-42. The reference further discloses that PEG-liposome has a longer retention time in the blood than the conventional liposomes (see column 4, lines 44-46 and Figure 9). The reference further discloses the composition is intended for intravenous administration and the polypeptide may be a peptide or a protein, such as superoxide dimutase, interferons (alpha, beta and gamma)…colony stimulating factors (M-CSF (macrophage), G-CSF (granulocyte), GM-CSF (granulocyte, macrophage)…(see column 3, lines 17-41 and claim 9). This meets the limitation of claims 42 and 46. The reference further teaches supplementation of cholesterol in the composition (see Tables 3 and 5). This meets the limitation of claim 38. The differences between the reference and the instant claims are that the reference does not teach a composition wherein protein or

polypeptide is not encapsulated in said colloidal particles and the reference does not teach carbamate-linked uncharged lipopolymer (aminopropanediol distearyol (DS)).

11. However, Collins et al teach G-CSF:phospholipids and MGDF:phospholipid compositions having increased stability, exhibiting increased shelf life, and capable of use in high temperature formulations and a novel delivery vehicles (see column 1, lines 12-16). Further, the reference discloses that the need exists for compositions which provide the benefit of being useful in formulations procedures requiring high temperature (e.g., incorporation of G-CSF and/or MGDF into polymers) as well as being used as novel delivery vehicles (e.g., oral administration of pegylated G-CSF) (see column 4, lines 3-8). The reference further discloses that rhG-CSF can insert into less efficiently into the phosphatidylethanolamines (PE's) and phosphatidylserines (PS's) (see column 16, lines 5-9 and Figures 5 and 6). Example 5 discloses the interaction of chemically modified G-CSF (pegylated G-CSF (PEG-G-CSF)) with negatively charged lipid vesicles (see column 17, lines 63-67). The reference discloses preparation of DMPG:PEG-G-CSF (17:1 mole/mole) (see column 18, lines 18-20) and PEG-G-CSF:DMPG (see column 18. line30-33).

12. Zalipsky S teaches that liposomes containing PEG-substituted neutral lipopoplymers provide similar circulation times to liposomes incorporating conventional, negatively charged PEG-substituted phospholipids. Further, the reference teaches that use of the uncharged lipopolymers can also present advantages in terms of interactions with cell surfaces and reduced leakage of charged substances, particularly cationic drugs, from the liposomes (see abstract). Furthermore, the reference discloses different

types of lipids (see column 3, lines 1-24) and the synthesis of PGE-Aminopropanediol distearoyl (see Example 1A).

13. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Martins et al and Collins et al and Zalipsky patents, since they Martins et al and Collins et al teach composition comprising G-CSF with liposome and pegylation and Zalipsky teaches that neutral PEG-lipopolymers and negatively charged PEG-phospholipids have similar circulation times. One of ordinary skill in the art would be motivated to combine the teachings since Collins et al teach that pegylated G-CSF can be used for oral administration and there is a need for compositions which provide the benefit of being useful in formulation procedures requiring high temperature (see column 4, lines 1-8). There is a reasonable expectation of success, since Collins et al teach that DMPG:PEG-G-CSF samples were found to fully recover secondary structure after heating, and a chemically modified PEG-G-CSF:DMPG also exhibited stabilizing effects (see column 18, lines 21-23 and 29-32).

14. Claims 47, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martins et al (US Patent # 5225212) and Collins et al (US Patent #5874075) and Zalipsky (US Patent # 6586001) as applied to claims 28-43 and 46 above, and further in view of Habberfield (PG Pub 2002/0099001) and (Tompkins et al, Nature Medicine, May 2002, 8(5): 451-453).

15. The instant claims are drawn to a method of treatment of a patient suffering from a disease (elected species: Multiple sclerosis) comprising administrating to said patient a pharmaceutical composition for parenteral administration comprising a therapeutically

effective amount of a protein or polypeptide (G-CSF) effective in the treatment of the disease and colloidal particles (amphipathic lipid derivatized with a biocompatible hydrophilic polymer).

16. The teachings of Martins et al and Collins et al and Zalipsky are described supra. The difference between the references and the instant claims is the reference does not teach multiple sclerosis.

17. However, Habberfield teaches compositions and method for oral delivery of chemically modified proteins, including chemically modified G-CSF and chemically modified consensus interferon. Uptake from the intestine to the bloodstream is demonstrated for pegylated G-CSF and pegylated consensus interferon (see abstract). Furthermore, the reference discloses that PEG-G-CSF can be administered intravenously for dosing (see paragraph [0115]). The reference further discloses that conditions such as cell proliferation disorders, viral infections and autoimmune disorders such as multiple sclerosis may be alleviated by administration of polymer/consensus interferon composition (see paragraph [0055]). The reference is silent as to G-CSF in alleviating multiple sclerosis.

18. Tompkins et al discloses treatment with G-CSF before the onset of MS disease decreased the severity of the early stages of the disease but had no effect later. As Tompkins et al discloses, Zavala et al showed decreased disease severity upon G-CSF treatment at the acute severity of disease (see p. 452, 3rd column, 1st paragraph).

19. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of the prior arts since Tompkins et al teach that G-CSF can be

used in treatment of MS, and Habberfield teaches compositions and method for oral delivery of chemically modified G-CSF and interferon that may be used to alleviate MS. One of ordinary skill in the art would be motivated to combine since Habberfield teaches that injection is not desirable, since recipient may experience discomfort or pain (see paragraph [0003]) and Habberfield teaches that the composition (PEG-G-CSF) can also be administered both parenterally and orally. Martins et al teach that liposome:PEG-protein composition is thermally stable. Therefore, there is a reasonable expectation of success, since G-CSF is used for treating MS and having liposome and PEG in a composition thermally stabilizes and PEGylation increases stability and circulation time of the therapeutic protein and decrease immunogenicity (see PG Pub 2002/0099001, paragraph [0014]).

Obvious Double Patenting

20. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

21. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

22. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 28-33 and 39-43 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 6930087 in view of Collins et al (US Patent # 5874075).

24. The claims of instant application are drawn to a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a therapeutic protein or polypeptide and substantially neutral colloidal particles (a mean particle diameter of between a, the particles about 0.03 to about 0.4 micron, preferred 0.1 micron) comprising approximately 1-20 mol percent of an amphipathic lipid (PE, phospholipids from natural or synthetic sources) derivatized with a biocompatible polymer (PEG, about 500 to about 5000 daltons, preferred 2000 daltons), the polymer carrying substantially no net charge wherein the protein is not encapsulated in the colloidal particles.

25. The US Patent '087 teaches a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a therapeutic protein or polypeptide and substantially neutral colloidal particles (having a mean particle diameter of about 0.05 to about 0.4 microns, preferred 0.1 micron), the particles comprising approximately 1-20 mol percent of an amphipathic lipid (PE, natural or synthetic phospholipids) derivatized with a biocompatible hydrophilic polymer (PEG, about 1000

to about 5000 daltons, preferred 2000 daltons), the polymer carrying substantially no net charge, wherein the protein or polypeptide is not encapsulated in the colloidal particle is not encapsulated in the colloidal particle. The difference between the reference and the instant claims is that the reference does not disclose G-CSF.

26. However, Collins et al teach G-CSF:phospholipids and MGDF:phospholipid compositions having increased stability, exhibiting increased shelf life, and capable of use in high temperature formulations and a novel delivery vehicles (see column 1, lines 12-16). Further, the reference discloses that the need exists for compositions which provide the benefit of being useful in formulations procedures requiring high temperature (e.g., incorporation of G-CSF and/or MGDF into polymers) as well as being used as novel delivery vehicles (e.g., oral administration of pegylated G-CSF) (see column 4, lines 3-8). The reference further discloses that rhG-CSF can insert into less efficiently into the phosphatidylethanolamines (PE's) and phosphatidylserines (PS's) (see column 16, lines 5-9 and Figures 5 and 6). Example 5 discloses the interaction of chemically modified G-CSF (pegylated G-CSF (PEG-G-CSF)) with negatively charged lipid vesicles (see column 17, lines 63-67). The reference discloses preparation of DMPG:PEG-G-CSF (17:1 mole/mole) (see column 18, lines 18-20) and PEG-G-CSF:DMPG (see column 18. line30-33).

27. Thus if one of ordinary skill in the art practiced claimed invention of the US Patent '087 in view of US Patent '075, one would necessarily achieve the claimed invention of the instant application. If one of ordinary skill in the art practiced the claims

of instant application, one would necessarily achieve the claimed invention of US Patent '087.

28. Claims 28-33 and 39-43 are rejected under 35 U.S.C. 103(a) as being obvious over Baru et al (US Patent # 6930087) in view of Collins et al (US Patent # 5874075). The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

29. The claims of instant application are drawn to a pharmaceutical composition for parenteral administration comprising a therapeutically effective amount of a therapeutic protein or polypeptide and substantially neutral colloidal particles (a mean particle

diameter of between a, the particles about 0.03 to about 0.4 micron, preferred 0.1 micron) comprising approximately 1-20 mol percent of an amphipathic lipid (PE, phospholipids from natural or synthetic sources) derivatized with a biocompatible polymer (PEG, about 500 to about 5000 daltons, preferred 2000 daltons), the polymer carrying substantially no net charge wherein the protein is not encapsulated in the colloidal particles.

30. The teachings of US Patent '087 are described above in paragraph 25. The difference between the reference and the instant claims is that the reference does not disclose G-CSF.

31. However, Collins et al teach G-CSF:phospholipids and MGDF:phospholipid compositions having increased stability, exhibiting increased shelf life, and capable of use in high temperature formulations and a novel delivery vehicles (see column 1, lines 12-16). Further, the reference discloses that the need exists for compositions which provide the benefit of being useful in formulations procedures requiring high temperature (e.g., incorporation of G-CSF and/or MGDF into polymers) as well as being used as novel delivery vehicles (e.g., oral administration of pegylated G-CSF) (see column 4, lines 3-8). The reference further discloses that rhG-CSF can insert into less efficiently into the phosphatidylethanolamines (PE's) and phosphatidylserines (PS's) (see column 16, lines 5-9 and Figures 5 and 6). Example 5 discloses the interaction of chemically modified G-CSF (pegylated G-CSF (PEG-G-CSF)) with negatively charged lipid vesicles (see column 17, lines 63-67). The reference discloses preparation of

DMPG:PEG-G-CSF (17:1 mole/mole) (see column 18, lines 18-20) and PEG-G-CSF:DMPG (see column 18. line30-33).

32. Thus if one of ordinary skill in the art practiced claims of US Patent '087 in view of US Patent '075, one would necessarily achieve the claimed invention of the instant application. Further, if one of ordinary skill in the art practiced the claims of instant application, one would necessarily achieve the claimed invention of the US Patent '087. Therefore, the US Patent '087 is obvious over the instant claims 28-33 and 39-43.

Conclusion

33. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Julie Ha whose telephone number is 571-272-5982. The examiner can normally be reached on Mon-Fri, 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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